Acute Mitochondrial Dysfunction after Mild Traumatic Brain Injury

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Traumatic brain injuries (TBIs) are a major societal and public health concern with over 1.7 million TBIs reported each year in the US. Mild TBIs (mTBIs), accounting for over 80% of TBIs, can cause cognitive and behavioral impairment. While it is known that mTBI does not cause widespread neuronal death, the mechanisms underlying neurological impairment and increased cellular susceptibility to subsequent head impacts are unknown. To investigate the hypothesis that altered mitochondrial bioenergetics following mTBI underlie cellular vulnerability to repeated insults, we employed a mouse model of closed head injury (CHI) to examine mitochondrial function after mTBI. A single CHI was produced by a pneumatically controlled impact device with a silicone tip at midline to model a bilateral diffuse injury. A novel object recognition (NOR) test was performed at 48 hours post-injury. Mitochondrial function was assayed from ventral (including entorhinal) cortex and hippocampus homogenates collected at 24 and 48 hours post-injury (n=3-6/group). Oxygen consumption rates (OCRs) were measured from isolated mitochondria using a Seahorse XF24 Flux Analyzer. At 48 hours post-injury, recognition memory was significantly impaired in the CHI group compared to sham ($p<0.05$). State III (ADP-mediated) respiration OCRs were significantly decreased in the hippocampal mitochondria of the CHI group compared to sham at 24 hours ($p < 0.01$) but not at 48 hours post-injury. Conversely, ventral cortex-derived mitochondria exhibited a delayed decrease in State III OCRs at 48 hours post-injury ($p<0.0001$). No significant differences were observed in other respiration states. This study establishes that mTBI associated with cognitive impairment results in early mitochondrial dysfunction which may have region-specific temporal characteristics. Future directions will aim to establish an expanded time course of mitochondrial bioenergetics.

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